

This Page Is Inserted by IFW Operations
and is not a part of the Official Record

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

**As rescanning documents *will not* correct images,
please do not report the images to the
Image Problem Mailbox.**

12

EUROPEAN PATENT APPLICATION

21 Application number: 89305370.2

22 Date of filing: 26.05.89

51 Int. Cl.4: C 07 D 471/06
C 07 D 487/06,
A 61 K 31/435,
A 61 K 31/415, A 61 K 31/55
/(C07D471/06,221:00,209:00)

30 Priority: 27.05.88 GB 8812636

43 Date of publication of application:
29.11.89 Bulletin 89/48

84 Designated Contracting States:
AT BE CH DE ES FR GB IT LI NL SE

71 Applicant: GLAXO GROUP LIMITED
Clarges House 6-12 Clarges Street
London W1Y 8DH (GB)

72 Inventor: Bays, David Edmund
9 Windmill Field
Ware Hertfordshire (GB)

Coates, Ian Harold
20 Mandeville Road
Hertford Hertfordshire (GB)

Bradshaw, John 1 Putty Hall Cottages
Shaftenhoe End Barley
Royston Hertfordshire (GB)

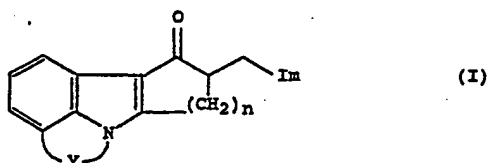
Mitchell, William Leonard
230 Barker Drive
London, NW1 0JF (GB)

74 Representative: Marchant, James Ian et al
Elkington and Fife Beacon House 113 Kingsway
London WC2B 6PP (GB)

Claims for the following Contracting State: ES.

54 Tetracyclic ketones.

57 The invention relates to tetracyclic ketones of the general formula (I)



wherein n represents 1, 2 or 3;
Im represents an imidazolyl group of the formula:



wherein one of the groups represented by R¹, R² and R³ is a hydrogen atom or a C₁-alkyl, C₃-cycloalkyl, C₃-alkenyl, phenyl or phenylC₁-alkyl group, and each of the other two

groups, which may be the same or different, represents a hydrogen atom or a C₁-alkyl group;
Y represents a group -(CH₂)_m, where m represents 2, 3 or 4, or a group -X(CH₂)_p, where p represents 2 or 3, X represents an oxygen or a sulphur atom or a group NR⁴, where R⁴ is a C₁-alkyl group, and X is attached to the benzene ring moiety of the molecule;
and physiologically acceptable salts and solvates thereof.

The compounds are potent and selective antagonists of the effect of 5-HT at 5-HT₃ receptors and are useful, for example, in the treatment of psychotic disorders, anxiety, and nausea and vomiting.

Description

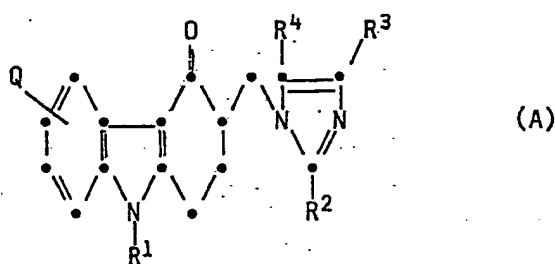
TETRACYCLIC KETONES

This invention relates to tetracyclic ketones, to processes for their preparation, to pharmaceutical compositions containing them and to their medical use.

In particular the invention relates to compounds which are potent and selective antagonists of 5-hydroxytryptamine (5-HT) at 5-HT receptors of the type located on terminals of primary afferent nerves. Receptors of this type are now designated as 5-HT₃ receptors and are also present in the central nervous system. 5-HT occurs widely in the neuronal pathways in the central nervous system and disturbance of these 5-HT containing pathways is known to alter behavioural syndromes such as mood, psychomotor activity, appetite and memory.

Compounds having antagonist activity at 5-HT₃ receptors have been described previously.

Thus for example published UK Patent Specification No. 2153821A and published European Patent Specifications Nos. 191562, 219193 and 210840 disclose 3-imidazolylmethyltetrahydrocarbazolones which may be represented by the general formula (A):



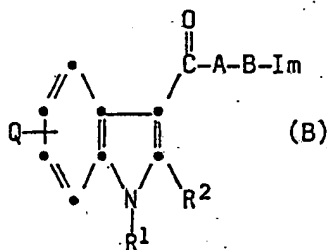
wherein R¹ represents a hydrogen atom or a group selected from C₁₋₁₀alkyl, C₃₋₆alkenyl, C₃₋₁₀alkynyl, C₃₋₇cycloalkyl, C₃₋₇cycloalkylC₁₋₄alkyl, phenyl or phenylC₁₋₃alkyl, and in the case where Q represents a hydrogen atom, R¹ also represent -CO₂R⁵, -COR⁵, -CONR⁵R⁶ or -SO₂R⁵ (wherein R⁵ and R⁶, which may be the same or different, each represents a hydrogen atom, a C₁₋₆alkyl or C₃₋₇cycloalkyl group, or a phenyl or phenylC₁₋₄alkyl group, in which the phenyl group is optionally substituted by one or more C₁₋₄alkyl, C₁₋₄alkoxy or hydroxy groups or halogen atoms, with the proviso that R⁵ does not represent a hydrogen atom when R¹ represents a group -CO₂R⁵ or -SO₂R⁵);

one of the groups represented by R², R³ and R⁴ is a hydrogen atom or a C₁₋₆alkyl, C₃₋₇cycloalkyl, C₂₋₆alkenyl, or phenylC₁₋₃alkyl group, and each of the other two groups, which may be the same or different, represents a hydrogen atom or a C₁₋₆alkyl group;

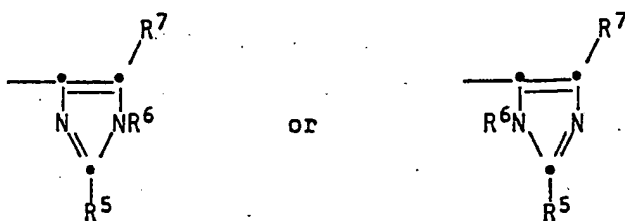
Q represents a hydrogen atom or a halogen atom or a hydroxy, C₁₋₄alkoxy, phenylC₁₋₃alkoxy or C₁₋₆alkyl group or a group -NR⁷R⁸ or -CONR⁷R⁸ (wherein R⁷ and R⁸, which may be the same or different, each represents a hydrogen atom or a C₁₋₄alkyl or C₃₋₄alkenyl group, or together with the nitrogen atom to which they are attached form a saturated 5 to 7 membered ring);

and physiologically acceptable salts and solvates thereof.

Furthermore, published European Patent Specification No. 242973 discloses ketone derivatives which may be represented by the general formula (B):



wherein Im represents an imidazolyl group of formula:



Q represents a hydrogen atom;

R¹ represents a hydrogen atom or a C₁₋₆alkyl, C₃₋₆alkenyl, C³⁻¹⁰alkynyl, C³⁻⁷cycloalkyl, C³⁻⁷cycloalkylC₁₋₄alkyl, phenyl or phenylC₁₋₃alkyl group;

R₂ represents a hydrogen atom or a C₁₋₆alkyl, C₃₋₆alkenyl, C₃₋₇cycloalkyl, phenyl or phenylC₁₋₃alkyl group;

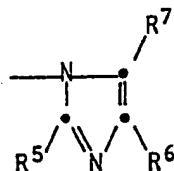
A-B represents the group R³R⁴C-CH₂ or R³C=CH;

R³ and R⁴, which may be the same or different, each represents a hydrogen atom or a C₁₋₆alkyl group;

one of the groups represented by R⁵, R⁶ and R⁷, is a hydrogen atom or a C₁₋₆alkyl, C₃₋₇cycloalkyl, C₃₋₆alkenyl, phenyl or phenylC₁₋₃alkyl group, and each of the other two groups, which may be the same or different, represents a hydrogen atom or a C₁₋₆alkyl group;

and physiologically acceptable salts and solvates thereof.

Published European Patent Specification No. 266899 discloses ketone derivatives which may also be represented by the general formula (B), but wherein Im represents an imidazolyl group of formula:



wherein R⁵, R⁶ and R⁷ are as defined in EPA 242973, although one of these groups may additionally represent a vinyl group;

R¹ is as defined in EPA 242973, although one of these groups may additionally represent a group selected from -CO₂R¹⁰, -COR¹⁰, -CONR¹⁰R¹¹ or -SO₂R¹⁰ (wherein R¹⁰ and R¹¹, which may be the same or different, each represents a hydrogen atom, a C₁₋₆alkyl or C₃₋₇cycloalkyl group, or a phenyl or phenylC₁₋₄alkyl group, in which the phenyl group is optionally substituted by one or more C₁₋₄alkyl, C₁₋₄alkoxy or hydroxy groups or halogen atoms, with the proviso that R¹⁰ does not represent a hydrogen atom when R¹ represents a group -CO₂R¹⁰ or -SO₂R¹⁰);

R₂ is as defined in EPA 242973;

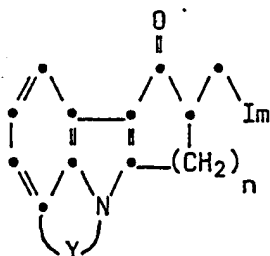
A-B represents the group R³R⁴C-CH₂ wherein R³ and R⁴ are as defined in EPA 242973;

Q is as defined in formula (A);

and physiologically acceptable salts and solvates thereof.

We have now found a novel group of compound which differ in structure from those described previously, and which are potent antagonists of the effect of 5-HT at 5-HT₃ receptors.

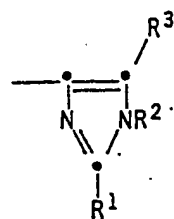
Thus the present invention provides a tetracyclic ketone of the general formula (I):



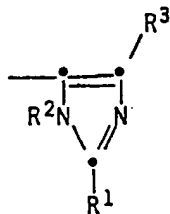
(I)

wherein n represents 1, 2 or 3;

Im represents an imidazolyl group of the formula:



or



wherein one of the groups represented by R¹, R² and R³ is a hydrogen atom or a C₁₋₆alkyl, C₃₋₇cycloalkyl, C₃₋₆alkenyl, phenyl or phenylC₁₋₃alkyl group, and each of the other two groups, which may be the same or different, represents a hydrogen atom or a C₁₋₆alkyl group;

Y represents a group -(CH₂)_m-, where m represents 2, 3 or 4, or a group -X(CH₂)_p-, where p represents 2 or 3;

X represents an oxygen or a sulphur atom or a group NR⁴, where R⁴ is a C₁₋₆alkyl group, and X is attached to the benzene ring moiety of the molecule;

and physiologically acceptable salts and solvates thereof.

Suitable physiologically acceptable salts of the compounds of general formula (I) include acid addition salts formed with organic or inorganic acids for example, hydrochlorides, hydrobromides, sulphates, alkyl or aryl sulphonates (e.g. methanesulphonates or p-toluenesulphonates), phosphates, citrates, succinates, tartrates, acetates, fumarates and maleates. The solvates may, for example, be hydrates.

It will be appreciated that the carbon atom between the carbonyl group and the group $-(CH_2)_n-$ is asymmetric and may exist in the R- or S- configuration. Furthermore, depending on the nature of the substituents R^1 , R^2 , R^3 and R^4 , centres of optical and geometric isomerism may occur elsewhere in the molecule. All optical isomers of compounds of general formula (I) and their mixtures including the racemic mixtures thereof, and all the geometric isomers of compounds of formula (I), are embraced by the invention.

Referring to the general formula (I), an alkyl group may be a straight chain or branched chain alkyl group, for example, methyl, ethyl, propyl, prop-2-yl, butyl, but-2-yl, 2-methylprop-2-yl, pentyl, pent-3-yl or hexyl. A C₃₋₆alkenyl group may be, for example, a propenyl or butenyl group. When R^2 represents a C₃₋₆alkenyl group, the double bond may not be adjacent to the nitrogen atom. A phenylC₁₋₃alkyl group may be, for example, a benzyl, phenethyl or 3-phenylpropyl group. A C₃₋₇cycloalkyl group may be, for example, a cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl group.

A preferred class of compounds of formula (I) is that in which R^1 , R^2 and R^3 each independently represent a hydrogen atom or a C₁₋₄alkyl (e.g. methyl) group. A further preferred class of compounds is that wherein R^1 and R^2 each represent a hydrogen atom, and R^3 is a C₁₋₃alkyl (e.g. methyl) group.

Another preferred class of compounds of formula (I) is that in which Y represents the group $-(CH_2)_3-$.

Another preferred class of compounds of formula (I) is that in which n represents 2.

A preferred compound according to the invention is 5, 6, 9, 10-tetrahydro-10-[(5-methyl-1H-imidazol-4-yl)methyl]-4H-pyrido[3,2,1-jk]carbazol-11(8H)-one and its physiologically acceptable salts and solvates.

The potent and selective antagonism of 5-HT at 5-HT₂ receptors by the compounds of the invention may be demonstrated by their ability to inhibit 3-(5-methyl-1H-imidazol-4-yl)-1-[1-(methyl-t³)-1H-indol-3-yl]-1-propanone binding in rat entorhinal cortex homogenates (following the general procedure described by G. Kilpatrick et al. in *Nature*, 1987, 330, 746); and/or by their ability to inhibit the 5-HT-induced depolarisation of the rat isolated vagus nerve preparation.

Compounds of formula (I), which antagonise the effect of 5-HT at 5-HT₂ receptors, are useful in the treatment of conditions such as psychotic disorders (e.g. schizophrenia and mania); anxiety; and nausea and vomiting, particularly that associated with cancer chemotherapy and radiotherapy. Compounds of formula (I) are also useful in the treatment of gastric stasis; symptoms of gastrointestinal dysfunction such as occur with dyspepsia, peptic ulcer, reflux oesophagitis, flatulence and irritable bowel syndrome; migraine; and pain. Compounds of formula (I) may also be used in the treatment of dependency on drugs and substances of abuse, depression, and dementia and other cognitive disorders.

According to another aspect, the invention provides a method of treatment of a human or animal subject suffering from a psychotic disorder such as schizophrenia or mania; or from anxiety; nausea or vomiting; gastric stasis; symptoms of gastrointestinal dysfunction such as dyspepsia, reflux oesophagitis, peptic ulcer, flatulence and irritable bowel syndrome; migraine; pain; dependency on drugs or substances of abuse; depression; or dementia or another cognitive disorder, which comprises administering an effective amount of a compound of formula (I) or a physiologically acceptable salt or solvate thereof.

Accordingly, the invention also provides a pharmaceutical composition which comprises at least one compound selected from compounds of the general formula (I), and their physiologically acceptable salts and solvates (e.g. hydrates), for use in human or veterinary medicine, and formulated for administration by any convenient route.

Such compositions may be formulated in conventional manner using one or more physiologically acceptable carriers and/or excipients.

Thus the compounds according to the invention may be formulated for oral, buccal, parenteral or rectal administration or in a form suitable for administration by inhalation or insufflation (either through the mouth or nose).

For oral administration, the pharmaceutical compositions may take the form of, for example, tablets or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (e.g. pregelatinised maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose); fillers (e.g. lactose, microcrystalline cellulose or calcium hydrogen phosphate); lubricants (e.g. magnesium stearate, talc or silica); disintegrants (e.g. potato starch or sodium starch glycolate); or wetting agents (e.g. sodium lauryl sulphate). The tablets may be coated by methods well known in the art. Liquid preparations for oral administration may take the form of, for example, solutions, syrups or suspensions, or they may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents (e.g. sorbitol-syrup, cellulose derivatives or hydrogenated edible fats); emulsifying agents (e.g. lecithin or acacia); non-aqueous vehicles (e.g. almond oil, oily esters, ethyl alcohol or fractionated vegetable oils); and preservatives (e.g. methyl or propyl-p-hydroxybenzoates or sorbic acid). The preparations may also contain buffer salts, flavouring, colouring and sweetening agents as appropriate.

Preparations for oral administration may be suitably formulated to give controlled release of the active compound.

For buccal administration the compositions may take the form of tablets or lozenges formulated in conventional manner.

The compounds of the invention may be formulated for parenteral administration by bolus injection or continuous infusion. Formulations for injection may be presented in unit dosage form e.g. in ampoules or in multi-dose containers, with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilising and/or dispersing agents. Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, e.g. sterile pyrogen-free water, before use.

The compounds of the invention may also be formulated in rectal compositions such as suppositories or retention enemas, e.g. containing conventional suppository bases such as cocoa butter or other glycerides.

In addition to the formulations described previously, the compounds of the invention may also be formulated as depot preparations. Such long acting formulations may be administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compounds of the invention may be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

For administration by inhalation the compounds according to the invention are conveniently delivered in the form of an aerosol spray presentation from pressurised packs or a nebuliser, with the use of a suitable propellant, e.g. dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a pressurised aerosol the dosage unit may be determined by providing a valve to deliver a metered amount. Capsules and cartridges of e.g. gelatin for use in an inhaler or insufflator may be formulated containing a powder mix of a compound of the invention and a suitable powder base such as lactose or starch.

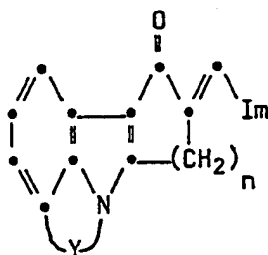
For intranasal administration, the compounds according to the invention may be formulated as solutions for administration via a suitable metered or unit dose device or alternatively as a powder mix with a suitable carrier for administration using a suitable delivery device.

The compounds of formula (I) may also be administered in combination with other therapeutic agents. Thus, for example, in the treatment of gastric stasis, symptoms of gastrointestinal dysfunction and nausea and vomiting, the compounds of formula (I) may be administered in combination with antisecretory agents such as histamine H₂-receptor antagonists (e.g. ranitidine, sufofodine or 1-methyl-5-[[3-[(1-piperidinylmethyl)phenoxy]propyl]amino]-1H-1,2,4-triazole-3-methanol, cimetidine, famotidine, nizatidine or roxatidine) or H⁺K⁺ATPase inhibitors (e.g. omeprazole). In the treatment of nausea and vomiting, compounds of formula (I) may also be administered in combination with dexamethasone.

A proposed dose of the compounds of the invention for administration to man (of approximately 70kg body weight) is 0.001 to 100mg, preferably 0.01 to 50mg, of the active ingredient per unit dose expressed as the weight of free base, which could be administered, for example, 1 to 4 times per day. It will be appreciated that it may be necessary to make routine variations to the dosage, depending on the age and condition of the patient. The dosage will also depend on the route of administration.

Compounds of general formula (I) and physiologically acceptable salts or solvates thereof may be prepared by the general methods outlined hereinafter. In the following description, the groups R¹ to R³, n, Y and Im are as defined for compounds of general formula (I) unless otherwise stated.

According to a first general process (A) a compound of general formula (I) may be prepared by hydrogenation of a compound of formula (II):



(II)

or a protected derivative thereof, followed where necessary by removal of any protecting groups.

Hydrogenation according to general process (A) may be effected using conventional procedures, for example using hydrogen in the presence of a noble metal catalyst (e.g. palladium, Raney nickel, platinum or rhodium). The catalyst may be supported on, for example, charcoal or alumina, or alternatively a homogeneous catalyst such as tris(triphenylphosphine)rhodium chloride may be used. The hydrogenation will generally be effected in a solvent such as an alcohol (e.g. methanol or ethanol), an ether (e.g. dioxan), or an ester (e.g. ethyl acetate), or in a mixture of an alcohol and either a hydrocarbon (e.g. toluene) or a halogenated hydrocarbon (e.g. dichloromethane), and at a temperature in the range -20 to +100°C, preferably 0 to 50°C.

Compounds of formula (II) are novel compounds and constitute a further aspect of the invention.

According to another general process (B), a compound of general formula (I) may be converted into another compound of formula (I) using conventional techniques. Such conventional techniques include hydrogenation

and alkylation using protection and deprotection where necessary.

Thus, according to one embodiment of the interconversion process (B), hydrogenation may be used to convert an alkenyl substituent into an alkyl substituent. Hydrogenation according to general process (B) may be effected using conventional procedures, for example, using hydrogen in the presence of a catalyst, as described above for general process (A).

The term 'alkylation' according to general process (B) includes the introduction of groups, such as cycloalkyl, alkenyl or phenalkyl groups.

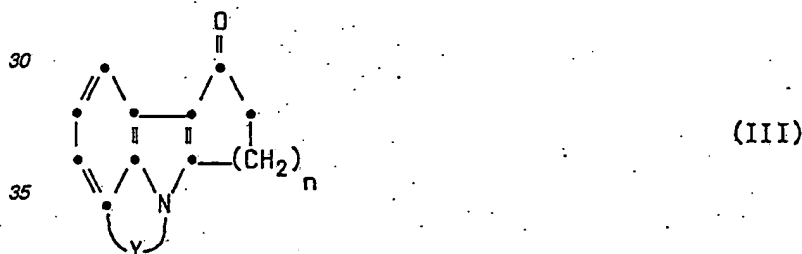
Thus, for example, a compound of formula (I) in which R^2 represents a C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{3-6} alkenyl or phenyl- C_{1-3} alkyl group may be prepared by alkylating the corresponding compound of formula (I) in which R^2 represents a hydrogen atom, using conventional procedures, for example as described in published European Patent specification No. 242973. Thus the reactions may be effected using an appropriate alkylating agent of formula R^5Z (where R^5 is the group to be introduced and Z is a leaving atom or group), preferably in the presence of a base.

It should be appreciated that in the above transformations it may be necessary or desirable to protect any sensitive groups in the molecule of the compound in question to avoid undesirable side reactions. For example, it may be necessary to protect the imidazole nitrogen atom, for example with an arylmethyl (e.g. trityl), alkyl (e.g. t-butyl), alkoxymethyl (e.g. methoxymethyl), acyl (e.g. benzyloxycarbonyl) or a sulphonyl (e.g. N,N-dimethylaminosulphonyl or p-toluenesulphonyl) group.

Thus according to another general process (C), a compound of general formula (I) may be prepared by the removal of any protecting groups from a protected form of a compound of formula (I). Deprotection may be effected using conventional techniques such as those described in 'Protective Groups in Organic Synthesis' by T. W. Greene (John Wiley and Sons, 1981).

For example, a trityl group may be cleaved by acid hydrolysis (e.g. using dilute hydrochloric or acetic acid). An alkoxyalkyl group may be removed using a mineral acid (e.g. dilute hydrochloric acid). An acyl group may be removed by hydrolysis under acidic or basic conditions (e.g. using hydrogen bromide or sodium hydroxide). A sulphonyl group may be removed by alkaline hydrolysis.

Compounds of formula (II) may be prepared by condensing a compound of formula (III):

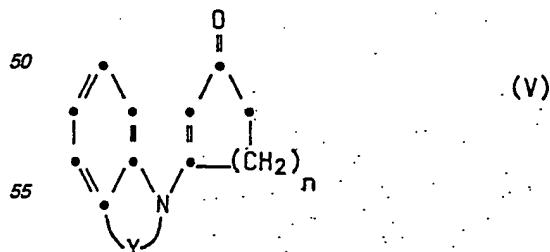


with a compound of formula (IV):

OHC-Im (IV)

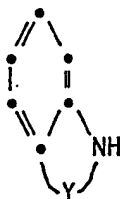
or a protected derivative thereof, in the presence of a base such as an alkali metal amide (e.g. lithium diisopropylamide) in an inert solvent such as an ether (e.g. tetrahydrofuran), followed by dehydration. The dehydration process may be effected using conventional methods, for example by using an organic or mineral acid (e.g. p-toluenesulphonic, methanesulphonic, trifluoroacetic or hydrochloric acid) in a suitable solvent such as an ether (e.g. tetrahydrofuran), an alcohol (e.g. methanol), or glacial acetic acid, at a temperature in the range 0 to 100°C.

Compounds of formula (III) may be prepared, for example, by the cyclisation of a compound of formula (V):



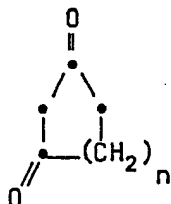
using methods analogous to that described by H. Iida et al. in J. Org. Chem., 1980, 45, 2938.

Compounds of formula (V) may be prepared, for example, by the reaction of a compound of formula (VI):



(VI)

with a compound of formula (VII):



(VII)

at an elevated temperature.

Compounds of formula (VI) are either known, or may be prepared from known compounds by conventional procedures.

Compounds of formula (IV) and protected derivatives thereof may be prepared, for example, by the method described in published European Patent Specification No. 242973A.

Where it is desired to isolate a compound of the invention as a salt, for example a physiologically acceptable salt, this may be achieved by reacting the compound of formula (I) in the form of the free base with an appropriate acid, preferably with an equivalent amount, in a suitable solvent such as an alcohol (e.g. ethanol or methanol), an aqueous alcohol (e.g. aqueous ethanol), a halogenated hydrocarbon (e.g. dichloromethane), an ester (e.g. ethyl acetate) or an ether (e.g. tetrahydrofuran).

Physiologically acceptable salts may also be prepared from other salts, including other physiologically acceptable salts, of the compound of formula (I) using conventional methods.

Individual enantiomers of the compounds of the invention may be obtained by resolution of a mixture of enantiomers (e.g. a racemic mixture) using conventional means, such as an optically active resolving acid; see for example 'Stereochemistry of Carbon Compounds' by E.L. Eliel (McGraw Hill, 1962) and 'Tables of Resolving Agents' by S. H. Wilen.

The methods described above for preparing the compounds of the invention may be used for the introduction of the desired groups at any stage in the stepwise formation of the required compounds, and it will be appreciated that these methods can be combined in different ways in such multi-stage processes. The sequence of the reactions in multi-stage processes should of course be chosen so that the reaction conditions used do not affect groups in the molecule which are desired in the final product.

The invention is further illustrated by the following Intermediates and Example. All temperatures are in °C. Thin layer chromatography (t.l.c.) was carried out on silica, and flash column chromatography (FCC) on silica (Merck 9385). Solvent System A as used for chromatography denotes dichloromethane:ethanol:0.88 ammonia solution (200:10:1). Organic extracts were dried over magnesium sulphate. The following abbreviations were used: THF -tetrahydrofuran; DMF - dimethylformamide.

Intermediate 1

3-(1,2,3,4-Tetrahydro-1-quinoliny)-2-cyclohexen-1-one

A mixture of 1,2,3,4-tetrahydroquinoline (5g) and 1,3-cyclohexanedione (4.21g) was heated at ca. 150° for 5h. The cooled reaction mixture was purified by FCC eluting with ethyl acetate to give the title compound (1.33g) as an oil, t.l.c. (ethyl acetate) Rf 0.34.

Intermediate 2

5,6,9,10-Tetrahydro-4H-pyrido[3,2,1-jk]carbazol-11(8H)-one

Cupric acetate (878mg) was added to a solution of 3-(1,2,3,4-tetrahydro-1-quinoliny)-2-cyclohexen-1-one (500mg) and palladium (II) acetate (100mg) in dry DMF (10mL). The mixture was heated at 135° under nitrogen for 3h, cooled, poured into water (100mL) and extracted with ethyl acetate (4x50mL). The combined, dried, organic extracts were evaporated to give a solid (ca. 490mg) which was purified by FCC eluting with ethyl acetate:hexan (2:1) to give the title compound (285mg), m.p. 160-164°.

Intermediate 3

(E)-5,6,9,10-Tetrahydro-10-[(5-methyl-1H-imidazol-4-yl)methylene]-4H-pyrido[3,2,1-jk]carbazol-11(8H)-one
 n-Butyllithium (1.73M in hexane: 4.14mL) was added dropwise to a cold (-70°) stirred solution of
 5 disisopropylamine (1mL) in dry THF (10mL) under nitrogen. The resulting solution was stirred at 0° for 30 min,
 cooled to -70° and added dropwise to a cold (-70°) stirred suspension of 5,6,9,10-tetrahydro-
 4H-pyrido[3,2,1-jk]carbazol-11(8H)-one (645mg) in dry THF (20mL) under nitrogen. The solution was allowed
 10 to reach 0° over 1h, cooled to -70° and a solution of 5-methyl-1-(triphenylmethyl)-1H-imidazole-4-carboxalde-
 hyde (1.01g) in dry THF (10mL) was added dropwise. The stirred mixture was allowed to reach room
 temperature over 2h, and then stirred for a further 3h. The solution was cooled to -70° and treated with acetic
 acid (8mL) and p-toluenesulphonic acid (5.44g) and heated at reflux for 16h. The solvent was removed in
 vacuo, the residue was treated with 8% sodium bicarbonate solution (150mL) and extracted with
 dichloromethane (4x50mL). The combined, dried organic extracts were evaporated to give a gum (c. 2g) which
 was purified by FCC eluting with System A to give the title compound (145mg) as a solid, m.p. 260-264°.

Example 1

5,6,9,10-Tetrahydro-10-[(5-methyl-1H-imidazol-4-yl)methyl]-4H-pyrido[3,2,1-jk]carbazol-11(8H)-one maleate
 A solution of (E)-5,6,9,10-tetrahydro-10-[(5-methyl-1H-imidazol-4-yl)methylene]-4H-pyrido[3,2,1-jk]carba-
 20 zol-11(8H)-one (135mg) in ethanol (10mL) was added to a suspension of pre-reduced 10% palladium oxide on
 carbon catalyst (50% aqueous paste; 75mg) in ethanol (3mL) and hydrogenated at room temperature and
 atmospheric pressure for 5h. The mixture was then filtered and evaporated to give a gum (ca. 150mg) which
 was purified by FCC eluting with System A to give an oil (118mg). This was dissolved in dichloromethane
 (ca. 2mL) and treated with a solution of maleic acid (44mg) in absolute ethanol (0.5mL). The solvent was
 25 removed in vacuo and the residue was triturated with dry ether (5 x 5mL) to give the title compound (142mg) as
 a solid, m.p. 190-192°.

Water Analysis Found 0.54% w/w \equiv 0.13mol H₂O.

Analysis Found

C,65.5; H,5.9; N,9.4;

C₂₀H₂₁N₃O₄. 0.13 H₂O requires

C,65.8; H,5.8; N,9.6%.

The following examples illustrate pharmaceutical formulations according to the invention. The term "active
 35 ingredient" is used herein to represent a compound of formula (I).

TABLETS FOR ORAL ADMINISTRATION

Tablets may be prepared by the normal methods such as direct compression or wet granulation.

40 The tablets may be film coated with suitable film forming materials, such as hydroxypropyl methylcellulose,
 using standard techniques. Alternatively the tablets may be sugar coated.

Tablets of other strengths may be prepared by altering the ratio of active ingredient to excipients or the
 compression weight and using punches to suit.

Direct Compression Tablet

	mg/tablet
Active Ingredient	0.50
Calcium Hydrogen	87.25
50 Phosphate BP*	
Croscarmellose	1.80
Sodium NF	
Magnesium Stearate	0.45
BP	
55 Compression weight	90.00

* of a grade suitable for direct compression.

60 The active ingredient is passed through a 60 mesh sieve, blended with the calcium hydrogen phosphate,
 croscarmellose, sodium and magnesium stearate. The resultant mix is compressed into tablets using a
 Manesty F3 tablet machine fitted with 5.5mm, flat bevelled dge punches.

INJECTION FOR INTRAVENOUS ADMINISTRATION

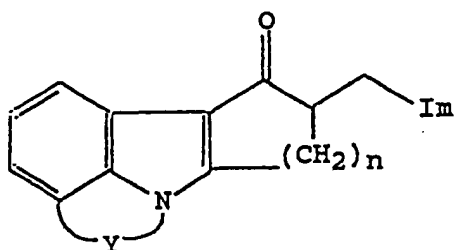
	<u>mg/ml</u>	
Active Ingredient	0.05	1.0
Sodium Chloride BP	as required	as required
Water for Injection BP to	1.0ml	1.0ml

Sodium chloride may be added to adjust the tonicity of the solution and the pH may be adjusted, using acid or alkali, to that of optimum stability and/or facilitate solution of the active ingredient. Alternatively, suitable buffer salts may be used.

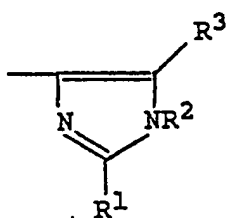
The solution is prepared, clarified and filled into appropriate size ampoules sealed by fusion of the glass. The injection is sterilised by heating in an autoclave using one of the acceptable cycles. Alternatively, the solution may be sterilised by filtration and filled into sterile ampoules under aseptic conditions. The solution may be packed under an inert atmosphere of nitrogen or other suitable gas.

Claims

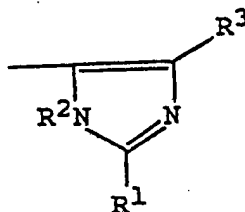
1. Compounds of the general formula (I)



wherein n represents 1, 2 or 3;
Im represents an imidazolyl group of the formula:



or



wherein one of the groups represented by R¹, R² and R³ is a hydrogen atom or a C₁₋₆alkyl, C₃₋₇cycloalkyl, C₃₋₆alkenyl, phenyl or phenylC₁₋₃alkyl group, and each of the other two groups, which may be the same or different, represents a hydrogen atom or a C₁₋₆alkyl group;
Y represents a group -(CH₂)_m-, where m represents 2, 3 or 4, or a group -X(CH₂)_p-, where p represents 2 or 3, X represents an oxygen or a sulphur atom or a group NR⁴, where R⁴ is a C₁₋₆alkyl group, and X is attached to the benzene ring moiety of the molecule;
and physiologically acceptable salts and solvates thereof.

2. Compounds as claimed in Claim 1 in which R¹, R² and R³ each independently represent a hydrogen atom or a C₁₋₄alkyl group.

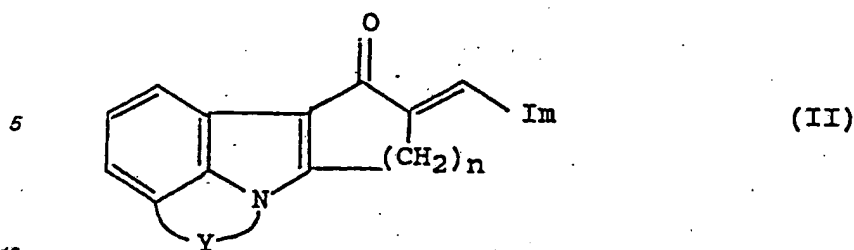
3. Compounds as claimed in Claim 1 in which R¹ and R² each represent a hydrogen atom, and R³ represents a C₁₋₃alkyl group.

4. Compounds as claimed in any of Claims 1 to 3 in which n is 2.

5. Compounds as claimed in any of claims 1 to 4 in which Y represents the group -(CH₂)₃-.

6. 5,6,9,10-Tetrahydro-10-[(5-methyl-1H-imidazol-4-yl)methyl]-4H-pyrido[3,2,1-j]carbazol-11(8H)-one and physiologically acceptable salts and solvates thereof.

7. A process for the preparation of compounds of general formula (I) as defined in any of Claims 1 to 6 or a physiologically acceptable salt or solvate thereof, which comprises:
(A) hydrogenating a compound of formula (II)



or a protected derivative thereof, followed if necessary by removal of any protecting groups present; or
(B) converting a compound of general formula (I) into another compound of formula (I) using conventional techniques; or

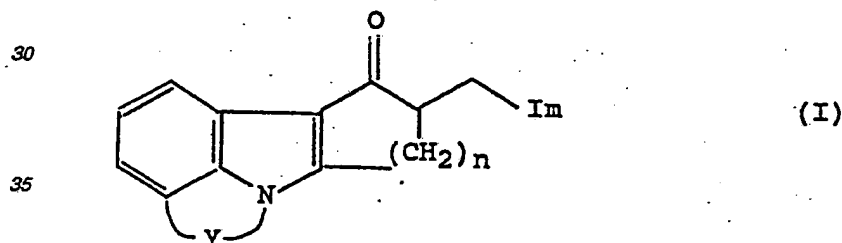
(C) removing protecting group(s) from a protected form of a compound of formula (I);
and when the compound of formula (I) is obtained as a mixture of enantiomers, optionally resolving the mixture to obtain the desired enantiomer;
and/or where the compound of formula (I) is in the form of a free base, optionally converting the free base into a salt.

8. A pharmaceutical composition comprising at least one compound of general formula (I) as defined in any of Claims 1 to 6 or a physiologically acceptable salt or solvate thereof together with at least one physiologically acceptable carrier or excipient.

9. A compound of formula (I) as defined in any of Claims 1 to 6 or a physiologically acceptable salt or solvate thereof for use as an active therapeutic agent.

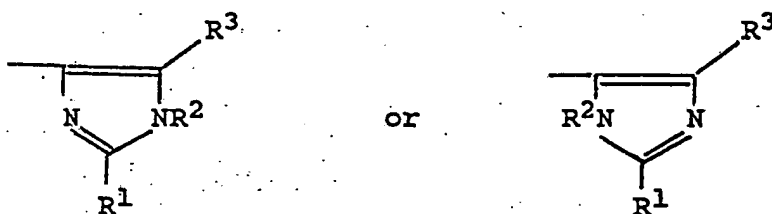
25 **Claims for the following Contracting State:ES**

1. A process for the preparation of compounds of the general formula (I)



wherein n represents 1, 2 or 3;

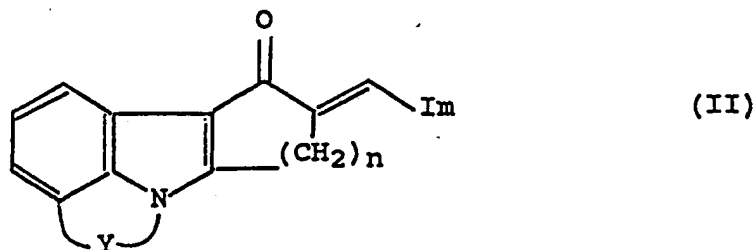
Im represents an imidazolyl group of the formula:



wherein one of the groups represented by R¹, R² and R³ is a hydrogen atom or a C₁₋₆alkyl, C₃₋₇cycloalkyl, C₃₋₆alkenyl, phenyl or phenylC₁₋₃alkyl group, and each of the other two groups, which may be the same or different, represents a hydrogen atom or a C₁₋₆alkyl group;

Y represents a group -(CH₂)_m-, where m represents 2, 3 or 4, or a group -X(CH₂)_p-, where p represents 2 or 3, X represents an oxygen or a sulphur atom or a group NR⁴, where R⁴ is a C₁₋₆alkyl group, and X is attached to the benzene ring moiety of the molecule;

and physiologically acceptable salts and solvates thereof, which comprises:
(A) hydrogenating a compound of formula (II)



or a protected derivative thereof, followed if necessary by removal of any protecting groups present; or
 (B) converting a compound of general formula (I) into another compound of formula (I) using conventional techniques; or
 (C) removing protecting group(s) from a protected form of a compound of formula (I);
 and when the compound of formula (I) is obtained as a mixture of enantiomers, optionally resolving the mixture to obtain the desired enantiomer;
 and/or where the compound of formula (I) is in the form of a free base, optionally converting the free base into a salt.

2. A process as claimed in Claim 1 for the preparation of compounds in which R^1 , R^2 and R^3 each independently represent a hydrogen atom or a C_{1-4} alkyl group.

3. A process as claimed in Claim 1 for the preparation of compounds in which R^1 and R^2 each represent a hydrogen atom, and R^3 represents a C_{1-3} alkyl group.

4. A process as claimed in any of Claims 1 to 3 for the preparation of compounds in which n is 2.

5. A process as claimed in any of claims 1 to 4 for the preparation of compounds in which Y represents the group $-(CH_2)_3-$.

6. A process as claimed in Claim 1 for the preparation of 5,6,9,10-tetrahydro-10-[(5-methyl-1H-imidazol-4-yl)methyl]-4H-pyrido[3,2,1-jk]carbazol-11(8H)-one and physiologically acceptable salts and solvates thereof.

19



Europäisches Patentamt
European Patent Office
Office européen des brevets

11

Publication number:

**0 344 015
A3**

12

EUROPEAN PATENT APPLICATION

21

Application number: 89305370.2

51

Int. Cl.⁵: C07D 471/06, C07D 487/06,
A61K 31/435, A61K 31/415,
A61K 31/55, //(C07D471/06,
221:00,209:00)

22

Date of filing: 26.05.89

30

Priority: 27.05.88 GB 8812636

43

Date of publication of application:
29.11.89 Bulletin 89/48

84

Designated Contracting States:
AT BE CH DE ES FR GB IT LI NL SE

88

Date of deferred publication of the search report:
18.07.90 Bulletin 90/29

71

Applicant: GLAXO GROUP LIMITED
Clarges House 6-12 Clarges Street
London W1Y 8DH(GB)

72

Inventor: Bays, David Edmund
9 Windmill Field

Ware Hertfordshire(GB)
Inventor: Coates, Ian Harold
20 Mandeville Road
Hertford Hertfordshire(GB)
Inventor: Bradshaw, John 1 Putty Hall
Cottages
Shaftenhoe End Barley
Royston Hertfordshire(GB)
Inventor: Mitchell, William Leonard
230 Barker Drive
London, NW1 0JF(GB)

74

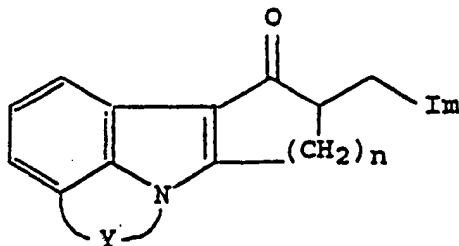
Representative: Marchant, James Ian et al
Elkington and Fife Beacon House 113
Kingsway
London WC2B 6PP(GB)

54

Tetracyclic ketones.

57

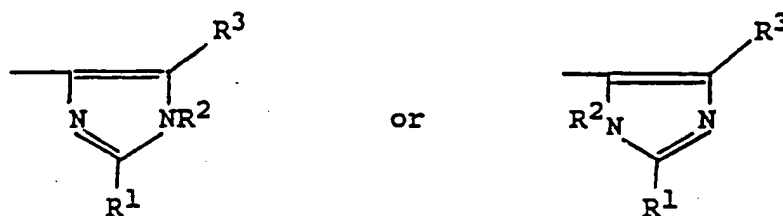
The invention relates to tetracyclic ketones of the general formula (I)



(I)

wherein n represents 1, 2 or 3;
Im represents an imidazolyl group of the formula:

EP 0 344 015 A3



wherein one of the groups represented by R^1 , R^2 and R^3 is a hydrogen atom or a C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{3-6} alkenyl, phenyl or phenyl C_{1-3} alkyl group, and each of the other two groups, which may be the same or different, represents a hydrogen atom or a C_{1-6} alkyl group;

Y represents a group $-(CH_2)_m-$, where m represents 2, 3 or 4, or a group $-X(CH_2)_p-$, where p represents 2 or 3, X represents an oxygen or a sulphur atom or a group NR^4 , where R^4 is a C_{1-6} alkyl group, and X is attached to the benzene ring moiety of the molecule;

and physiologically acceptable salts and solvates thereof.

The compounds are potent and selective antagonists of the effect of 5-HT at 5-HT₃ receptors and are useful, for example, in the treatment of psychotic disorders, anxiety, and nausea and vomiting.



European Patent
Office

EUROPEAN SEARCH REPORT

Application Number

EP 89 30 5370

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.4)
D,A	EP-A-0 242 973 (GLAXO) * Claims 1,11; page 5, lines 7-21 * ---	1,8	C 07 D 471/06 C 07 D 487/06
D,A	EP-A-0 191 562 (GLAXO) * Claims 1,9; page 3, lines 19-31 * ---	1,8	A 61 K 31/435 A 61 K 31/415 A 61 K 31/55 //
P,A	EP-A-0 297 651 (DUPHAR)(04-01-1989) * Claims 1,2; page 4, lines 7-20 * -----	1,8	(C 07 D 471/06 C 07 D 221:00 C 07 D 209:00)
			TECHNICAL FIELDS SEARCHED (Int. Cl.4)
			C 07 D 471/00 A 61 K 31/00
The present search report has been drawn up for all claims			
Place of search THE HAGUE		Date of completion of the search 25-04-1990	Examiner ALFARO I.
CATEGORY OF CITED DOCUMENTS X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document			